UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/827,368	04/20/2004	Shiv Kumar Agarwal	115683.01	3821

25944 7590 09/11/2006

OLIFF & BERRIDGE, PLC
P.O. BOX 19928
ALEXANDRIA, VA 22320

EXAMINER	
RAO, DEEPAK R	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 09/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/827,368	AGARWAL ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *4-13 and 18-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 14-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 10/409,045.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-36 are pending in this application.

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-3 and 14-17, in the reply filed on June 21, 2006 is acknowledged. The traversal is on the ground(s) that 'if the search and examination of an entire application can be made without a serious burden, the examiner must examine the subject matter of claims 1-8 and 14-36'. This is not found persuasive because the Groups have different class/subclasses and it would constitute a burden on the examiner to search the claimed subject matter in patent databases. Additionally, different fields of search would be required in the non-patent literature.

Inventions II-V and I are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case the compounds of formula (I) can be made using other materially different reagents and/or conditions. Also, the cyclization techniques used in the process can be used in making other materially different products.

Inventions I and XI-XIV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP

§ 806.05(h)). In the instant case the products may be used in different processes for example in pharmaceutical therapeutic use or agrochemical use. Also, the therapeutic methods can be practiced with other materially different products.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

> In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**
>
> Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Claims 4-13 and 18-36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on June 21, 2006.

Applicant's election of the species of Example 10 is acknowledged. The species reads on claims 1-3 and 14-17. The species represents a compound of formula (I) wherein:

X is O;

the rings represented by A and B are phenyl;

R1 and R_2 are each $-CH_3$;

R3 is H, R_4 is $-SCH_3$;

R5 is $-SCH_3$; and R6 is CN.

The guidelines in MPEP § 803.02 provide that upon examination if prior art is found for the elected species, the examination will be limited to the elected species.

Content of MPEP § 803.02 is provided here for convenience:

> As an example, in the case of an application with a Markush-type claim drawn to the compound C-R, wherein R is a radical selected from the group consisting of A, B, C, D and E, the examiner may require a provisional election of a single species, CA, CB, CC, CD or CE. The Markush-type claim would then be examined fully with respect to the elected species and any species considered to be clearly unpatentable over the elected species. If on examination the elected species is found to be anticipated or rendered obvious by prior art, the Markush-type claim and claims to the elected species shall be rejected, and claims to the non-elected species would be held withdrawn from further consideration. As in the prevailing practice, **a second action on the merits on the elected claims would be final.**
> On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. **The prior art search, however, will not be extended unnecessarily to cover all nonelected species.** Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action made final. Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry.

The elected species identically was not found in the prior art search and the search was expanded to the subgenus of formula (I) wherein:

X is O; R6 is CN; the rings A and B are phenyl; and R1-R5 are as defined in the claims and art was found.

As per the guidelines of MPEP § 803.02, the Markush-type claims were examined to the extent of the searched subgenus. The generic subject matter (i.e., all other definitions of X, R6, A and B) drawn to the non elected species from claims 1-2 and 14-15; and the species of claims 3 and 16-17 having substituents other than as indicated above are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected species.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 and 14-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound of formula (I) and the pharmaceutically acceptable salt thereof, does not reasonably provide enablement for their **derivatives**, their **analogs**, their **polymorphs**, etc. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working

examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The instant claims recite "Novel pyrimidine **derivatives** of the formula (I) ... their **derivatives**, their **analogs**, ... their **polymorphs**, and their pharmaceutically acceptable salts" wherein there is insufficient description in the specification regarding the types of **derivatives, analogs**, **polymorphs**, etc. intended by the recitation. The term 'derivative' or 'analog' generally represents any type of residue of a compound. The disclosure is with respect to compounds represented by formula (I) wherein the variables are as defined. The specification, however, does not provide what type of derivatives, analogs, etc. of the compounds of formula (I) are intended. The structural formula in the claim is a specific structural representation having specific defined substituent groups. There is no disclosure regarding any other derivatives or analogs of the compounds of formula (I) disclosed in the specification.

Factual Basis:

1. Specification has no working example of **polymorph** of compound of formula (I); and some of the exemplified compounds within the claimed genus were in contact with solvent. Yet they have not formed solvate as evident form spectral data provided for these compounds.
2. Searching the pertinent art in the related pyrimidine area did not result in support for such polymorphs of instant pyrimidine compounds.

   Further, the specification does not provide any explanation of what types of

'**polymorphs**' are intended, how these are made, etc. The existence, structure and the properties (e.g., stability, solubility, bioavilability, rate of dissolution, etc.) of polymorphs tend to be very unpredictable. In order to establish the most stable polymorphic form, each has to be characterized and screened individually using various analytical techniques such as X-ray diffraction, thermal analysis, particle morphology characterization, etc. In view of the lack of direction provided in the specification regarding the starting materials, the lack of working examples and the general unpredictability of chemical reactions, it would take an undue amount of experimentation for one skilled in the art to make the claimed compounds and therefore practice the invention. The starting material sources necessary to obtain the instant compounds must have been available as of the filing date in order to provide an enabling disclosure. See *In re Howarth*, 654 F.2d 103, 210 USPQ 689 (CCPA 1981); *Ex parte Moersch*, 104 USPQ 122 (POBA 1954).

Based on these two facts, a scope of enablement rejection follows using relevant Wands factors. Hence, the burden of establishing the *prime facie* case is met with.

a. **The nature of the invention and the state of the prior art:**

The compound of formula I embrace substituted pyrimidine compounds substituted with variable groups R5, R6 and rings A and B, which are further substituted with R^1, R^2, R^3, R^4. Careful calculation of the number of compounds embraced in the instant formula (I) shows a large number of compounds. The terms "derivatives", "analogs", "substituted groups", etc. embrace undefined number of variable groups and thus, the genus encompassed by the claims is excessively large and there is no teaching of any **polymorph** of this large genus.

A search in the general area of polymorphs resulted in Vippagunta et al., Advanced Drug

Delivery Reviews 48: 3-26, 2001, which clearly states that "The main challenge in managing the phenomenon of multiple solid forms of a drug is the inability to predict the number of forms that can be expected in a given case. This prediction would involve quantification of the myriad intermolecular forces within any proposed crystal structure as well as the ability to postulate the likely packing modes for a given molecule in all its configurations" (see page 11, col. 2).

Joachim Ulrich (Kirk-Othmer Encyclopedia of Chemical Technology) provides that "Pseudopolymorphs are solvates or in the case of water as solvent, hydrates, which means crystals that incorporate solvent molecules into the crystal lattice. Pseudopolymorphs exhibit different crystal forms and/or different densities, solubilities, dissolution rates, colors, hardnesses, etc. Compared with polymorphs, there is an additional degree of freedom (than temperature and pressure), which means a different solvent or even the moisture of the air that might change the stabile region of the pseudopolymorph".

b. **The predictability or lack thereof in the art:**

Hence the terms "derivative", "analog", "polymorph", etc. as applied to the above-mentioned compounds claimed by the applicant are not art-recognized compounds and hence there should be adequate enabling disclosure in the specification with working example(s).

c. **The amount of direction or guidance present:**

Examples illustrated in the experimental section are limited to making the compounds not related to polymorphs. There is no example of a polymorph of instant compound.

d. **The presence or absence of working examples:**

Determining if any particular substrate would form a polymorph would require synthesis of the substrate and subjecting it to crystallization with a variety of process conditions and other

parameters. The experimentation is potentially open-ended and there are no working examples of any type of polymorph of the instantly claimed compound.

The claims recite "polymorphs", yet the numerous examples presented all failed to produce a polymorph. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "[T]he specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there, is no evidence that such compounds exist... the examples of the patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, there should be showing supporting that solvates or polymorphs of these compounds exist and therefore can be made.

e. **The breadth of the claims & the quantity of experimentation needed:**

Specification provides no support, as noted above, for compounds generically embraced in the claim 1 would lead to desired polymorph of the compound of formula (I). As noted above, the genus embraces a large number of compounds and hence the claims are extremely broad. The quantity of experimentation needed would be an undue burden on skilled art in the chemical art since there is inadequate guidance given to the skilled artisan for the many reasons stated above. Even with the undue burden of experimentation, there is no guarantee that one would get the product of desired polymorph of compound of formula (I) embraced in the instant claims in view of the pertinent reference teachings.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3 and 14-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

1. The claims recite "**Novel** pyrimidones of the formula .... and their **derivatives**, their analogs, ... " through out the claims. The term 'novel' is not appropriate because the compounds are known in prior art documents. The plural recitation "pyrimidones" is not proper Markush language in a claim. The term "**derivative**" may be interpreted as a residue derived from the compounds of the claims, and it is confusing which compounds are derived from the compounds of formula (I). As the claims are drawn specifically to: 'A pyrimidone compound of formula (I)', it should be recited as such. Replacing the recitation "Novel pyrimidones" (in all occurrences) with -- A pyrimidone -- is suggested.
2. In claim 1, the recitation "carboxylic acid or its derivatives" is indefinite. The specification provides 'esters, amides, acid halides' as examples of the derivatives of carboxylic acid (see page 13, lines 21-22). The recitation however, contains open-ended language of "such as" and therefore, does not provide the metes and bounds of the term. Further, the claim already includes groups such as acyl, acylamino, alkoxycarbonyl, etc. as substituent groups which include functional groups such as 'an ester' and therefore, it is not clear what other 'derivative' of a carboxylic acid is intended by the recitation.
3. In claim 3, line 13 (sixth compound), in the recitation "b5-Cyano-2-...." it is not understood what is intended by the letter " b ".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

1. Claims 1-2 and 14-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Robev, CAPLUS Abstract 88:22768 (1978). The instant claims read on reference disclosed compounds, see the compounds having RN 65004-31-1; 65004-33-3; and 65229-67-6 disclosed in the enclosed copy of CAPLUS abstract. The proviso in claim 1 – "when R^1 represents hydrogen R^2 is not hydrogen" is noted. The proviso however is not applicable to the instant situation and the instant claims drawn to compounds of formula (I) wherein ring A is an unsubstituted ring continue to read on reference compounds 65004-31-1 and 65229-67-6 because in claim 1 when m is 0, R_2 is not present. The reference discloses the compound in a solvent and therefore, teaches a composition of the compound.
2. Claims 1-2 and 14-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Briel et al., CAPLUS Abstract 88:22768 (1978). The instant claims read on reference disclosed compound, see the compound having RN 101185-05-1 disclosed in the enclosed copy of CAPLUS abstract. The reference discloses the compound in a solvent and therefore, teaches a composition of the compound.
3. Claims 1-2 and 14-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Yokoyama et al., CAPLUS Abstract 107:7151 (1987). The instant claims read on reference disclosed compounds, see the compounds having RN 97242-70-1; 107427-92-

9; 107427-96-3; 107427-97-4; 107427-98-5; and 92742-69-8 disclosed in the enclosed copy of CAPLUS abstract. The proviso in claim 1 – "when R^1 represents hydrogen R^2 is not hydrogen" is noted. The proviso however is not applicable to the instant situation and the instant claims drawn to compounds of formula (I) wherein ring A is an unsubstituted ring continue to read on reference compounds because in claim 1 when m is 0, R_2 is not present. The reference discloses the compound in a solvent and therefore, teaches a composition of the compound.

4. Claims 1-2 and 14-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Mukherjee et al., CAPLUS Abstract 128:308465 (1998). The instant claims read on reference disclosed compounds, see the compounds disclosed in the enclosed copy of CAPLUS abstract. The proviso in claim 1 – "when R^1 represents hydrogen R^2 is not hydrogen" is noted. The proviso however is not applicable to the instant situation and the instant claims drawn to compounds of formula (I) wherein ring A is an unsubstituted ring continue to read on reference compounds because in claim 1 when m is 0, R_2 is not present. The reference discloses the compound in a solvent and therefore, teaches a composition of the compound.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deepak Rao
Primary Examiner
Art Unit 1624

September 5, 2006